

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 10 February 1998 (10.02.98)	
International application No. PCT/EP97/03549	Applicant's or agent's file reference 4-20937/A
International filing date (day/month/year) 04 July 1997 (04.07.97)	Priority date (day/month/year) 05 July 1996 (05.07.96)

Applicant

LANE, David et al.

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

21 January 1998 (21.01.98)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer S. De Michiel Telephone No.: (41-22) 338.83.38
---	---

PATENT COOPERATION TREATY

BEST AVAILABLE COPY PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

ROTH, Bernhard, M.
Novartis AG
Patent- und Markenabteilung
Lichtstrasse 35
CH-4002 Basel
SUISSE

Date of mailing (day/month/year) 15 April 1998 (15.04.98)	
Applicant's or agent's file reference 4-20937/A	IMPORTANT NOTIFICATION
International application No. PCT/EP97/03549	International filing date (day/month/year) 04 July 1997 (04.07.97)

1. The following indications appeared on record concerning:

the applicant the inventor the agent the common representative

Name and Address ROTH, Bernhard, M. Novartis AG Patent- und Markenabteilung Klybeckstrasse 141 CH-4002 Basel Switzerland	State of Nationality	State of Residence
	Telephone No.	
	061 324 31 67	
	Facsimile No.	
	061 322 75 32	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person the name the address the nationality the residence

Name and Address ROTH, Bernhard, M. Novartis AG Patent- und Markenabteilung Lichtstrasse 35 CH-4002 Basel Switzerland	State of Nationality	State of Residence
	Telephone No.	
	061 324 11 11	
	Facsimile No.	
	061 322 75 32	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Nicola Wolff Telephone No.: (41-22) 338.83.38
---	--

PATENT COOPERATION TREATY

SIC
13
BEST AVAILABLE COPY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 15 January 1999 (15.01.99)
Applicant's or agent's file reference 4-20937/A
International application No. PCT/EP97/03549

From the INTERNATIONAL BUREAU

To:

ROTH, Bernhard, M.
Novartis AG
Patent- und Markenabteilung
Lichtstrasse 35
CH-4002 Basel
SUISSE

IMPORTANT NOTIFICATION

International filing date (day/month/year) 04 July 1997 (04.07.97)

1. The following indications appeared on record concerning:

the applicant the inventor the agent the common representative

Name and Address BÖTTGER, Volker 6 Bridge Street Newport-on-Tay Fife DD6 8JJ United Kingdom	State of Nationality DE	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person the name the address the nationality the residence

Name and Address BÖTTGER, Volker Fichtenstrasse 88 D-82110 Germering-Unterpaffenhofen Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer S. De Michiel Telephone No.: (41-22) 338.83.38
---	---

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

ROTH, Bernhard, M.
 Novartis AG
 Patent- und Markenabteilung
 Lichtstrasse 35
 CH-4002 Basel
 SUISSE

Date of mailing (day/month/year) 15 January 1999 (15.01.99)			
Applicant's or agent's file reference 4-20937/A	IMPORTANT NOTIFICATION		
International application No. PCT/EP97/03549	International filing date (day/month/year) 04 July 1997 (04.07.97)		

1. The following indications appeared on record concerning:

the applicant the inventor the agent the common representative

Name and Address BÖTTGER, Angelika 6 Bridge Street Newport-on-Tay Fife DD6 8JJ United Kingdom	State of Nationality DE	State of Residence GB
Telephone No.		
Facsimile No.		
Teleprinter No.		

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person the name the address the nationality the residence

Name and Address BÖTTGER, Angelika Fichtenstrasse 88 D-82110 Germering-Unterpfaffenhofen Germany	State of Nationality DE	State of Residence DE
Telephone No.		
Facsimile No.		
Teleprinter No.		

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer S. De Michiel Telephone No.: (41-22) 338.83.36
---	---

PATENT COOPERATION TREATY

BEST AVAILABLE COPY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

09/214 371

ROTH, Bernhard, M.
 Novartis AG
 Patent- und Markenabteilung
 Lichtstrasse 35
 CH-4002 Basel
 SUISSE

Date of mailing (day/month/year) 13 January 1999 (13.01.99)	
Applicant's or agent's file reference 4-20937/A	IMPORTANT NOTIFICATION
International application No. PCT/EP97/03549	International filing date (day/month/year) 04 July 1997 (04.07.97)

1. The following indications appeared on record concerning:

the applicant the inventor the agent the common representative

Name and Address PICKSLEY, Stephen 52 Maule Street Carnoustie Angus DD7 6AB United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person the name the address the nationality the residence

Name and Address PICKSLEY, Stephen 54 Carr Bottom Road Greengates Bradford West Yorkshire BD10 0BD United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer S. De Michiel Telephone No.: (41-22) 338.83.38
---	---

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 13 January 1999 (13.01.99)	From the INTERNATIONAL BUREAU		
To:			
ROTH, Bernhard, M. Novartis AG Patent- und Markenabteilung Lichtstrasse 35 CH-4002 Basel SUISSE			
Applicant's or agent's file reference 4-20937/A	IMPORTANT NOTIFICATION		
International application No. PCT/EP97/03549	International filing date (day/month/year) 04 July 1997 (04.07.97)		

1. The following indications appeared on record concerning:

the applicant the inventor the agent the common representative

Name and Address BÖTTGER, Volker and BÖTTGER, Angelika 6 Bridge Street Newport-on-Tay Fife DD6 8JJ United Kingdom	State of Nationality DE	State of Residence GB
Telephone No.		
Facsimile No.		
Teleprinter No.		

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person the name the address the nationality the residence

Name and Address BÖTTGER, Volker and BÖTTGER, Angelika Fichtenstrasse 88 D-82110 Germering-Unterpaffenhofen Germany	State of Nationality DE	State of Residence DE
Telephone No.		
Facsimile No.		
Teleprinter No.		

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer S. De Michiel Telephone No.: (41-22) 338.83.38
---	---

PATENT COOPERATION TREATY

BEST AVAILABLE COPY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 13 January 1999 (13.01.99)
Applicant's or agent's file reference 4-20937/A
International application No. PCT/EP97/03549

From the INTERNATIONAL BUREAU

To:

ROTH, Bernhard, M.
Novartis AG
Patent- und Markenabteilung
Lichtstrasse 35
CH-4002 Basel
SUISSE

IMPORTANT NOTIFICATION

International filing date (day/month/year) 04 July 1997 (04.07.97)

1. The following indications appeared on record concerning:

the applicant the inventor the agent the common representative

Name and Address CHÈNE, Patrick 10, rue de Chalampe F-68100 Mulhouse France	State of Nationality FR	State of Residence FR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person the name the address the nationality the residence

Name and Address CHÈNE, Patrick 4, rue Sainte Geneviève F-68100 Mulhouse France	State of Nationality FR	State of Residence FR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer S. De Michiel Telephone No.: (41-22) 338.83.38
---	---

PATENT COOPERATION TREATY

BEST AVAILABLE COPY

PCT

COMMUNICATION OF
INTERNATIONAL APPLICATIONS
(PCT Article 20)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as designated Office

Date of mailing:

05 February 1998 (05.02.98)

The International Bureau transmits herewith copies of the international applications having the following international application numbers and international publication numbers:

International application no.:

PCT/EP97/03549

International publication no.:

WO98/01467

**CORRECTED VERSION
VERSION CORRIGEE**

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra
Telephone No.: (41-22) 338.83.38

1873203

CORRECTED
VERSION*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :	A3	(11) International Publication Number: WO 98/01467 (43) International Publication Date: 15 January 1998 (15.01.98)
(21) International Application Number:	PCT/EP97/03549	lampe, F-68100 Mulhouse (FR). FURET, Pascal [FR/FR]; 24, rue du Riegelsbourg, F-68800 Thann (FR).
(22) International Filing Date:	4 July 1997 (04.07.97)	(74) Agent: ROTH, Bernhard, M.; Novartis AG, Patent- und Markenabteilung, Klybeckstrasse 141, CH-4002 Basel (CH).
(30) Priority Data:	9614197.3 5 July 1996 (05.07.96) 9707041.1 7 April 1997 (07.04.97)	GB GB
(71) Applicants (<i>for all designated States except US</i>):	NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH). CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED [GB/GB]; 2 Carlton House Terrace, London SW1Y 5AR (GB).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(72) Inventors; and		Published
(75) Inventors/Applicants (<i>for US only</i>):	LANE, David [GB/GB]; Magicwell House, Balmullo, By Saint Andrews, Fife KY16 0AL (GB). BÖTTGER, Volker [DE/GB]; (GB). BÖTTGER, Angelika [DE/GB]; 6 Bridge Street, Newport-on-Tay, Fife DD6 8JJ (GB). PICKSLEY, Stephen [GB/GB]; 52 Maule Street, Carnoustie, Angus DD7 6AB (GB). HOCHKEPPEL, Heinz-Kurt [DE/CH]; Traugott Meyer-Strasse 1, CH-4147 Aesch (CH). GARCIA-ECHEVERRIA, Carlos [ES/CH]; Rennweg 98, CH-4052 Basel (CH). CHÈNE, Patrick [FR/FR]; 10, rue de Châ-	With international search report. <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(88) Date of publication of the international search report:		22 May 1998 (22.05.98)

(54) Title: INHIBITORS OF THE INTERACTION BETWEEN p53 AND MDM2

(57) Abstract

The present invention relates to compounds capable of binding to the oncogene protein MDM2, processes for the preparation of such compounds, pharmaceutical preparations comprising such compounds, and uses of said compounds, e.g. in the therapeutic (including prophylactic) treatment of an animal or especially of the human body. The present further relates to methods of and compounds for inhibiting the growth of tumor cells which comprise the wild type p53 suppressor by interfering with the interaction between human p53 and human MDM2.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

In. International Application No
PCT/EP 97/03549

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/47 C07K14/82 C12Q1/68 C12N15/11 A61K38/08

According to international Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 02642 A (UNIV DUNDEE ;PICKSLEY STEVEN MICHAEL (GB); LANE DAVID PHILIP (GB)) 1 February 1996 see page 3, line 20 - page 4, line 31 see example 3 see claims ---	1-18, 21-23
X	WO 93 20238 A (UNIV JOHNS HOPKINS) 14 October 1993 see claims 27-37 see the whole document ---	1-23 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"g" document member of the same patent family

2

Date of the actual completion of the international search

11 March 1998

Date of mailing of the international search report

08.04.98

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Cervigni, S

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/EP 97/03549

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S.M. PICKSLEY ET AL: "Immunochemical analysis of the interaction of p53 with MDM2" ONCOGENE, vol. 9, September 1994, pages 2523-2529, XP002058480 see page 2526 ---	1-10,12
X	J. LIN ET AL.: "Several hydrophobic amino acids in the p53 amino-terminal domain are required for transcriptional activation, binding to mdm-2 and the adenovirus 5 E1B 55-kD protein" GENES AND DEVELOPMENT, vol. 8, no. 10, May 1994, pages 1235-1246, XP002058481 see abstract see table 2 ---	1-10,12
P,X	V. BÖTTGER ET AL: "Identification of novel mdm2 binding peptides by phage display" ONCOGENE, XP002058482 see the whole document see page 2143, column 2, paragraph 4 - page 2143, paragraph 1; figure 5 ---	1-23
X	H. LEE ET AL: "Molecular characterisation of Nos-A" J. BACTERIOL., vol. 173, no. 17, September 1991, pages 5606-5413, XP002058483 * residues 462-471 * see figure 4 ---	3,6
X	WO 95 07934 A (CHIRON CORP) 23 March 1995 see page 3, line 30; claim 7 -----	6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 97/03549

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP 97/03549

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 1-9

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

In claims 1-2, the compounds are defined only by their capability to bind MDM2, feature not sufficient to allow a complete search.

In claims 2-9, the expression "derivatives thereof" is used in a too broad sense, consequently a complete search under Art 17(2) PCT was not possible. Therefore, the search has been directed to peptides as defined in claims 3-9, without taking in consideration any "derivative thereof".

Moreover, because of the high number of pertinent documents found in the prior art for the subject-matter of claim 6, only a few could be cited.

Remark : Although claims 17-22 and at least in part 10,12,13 and 23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

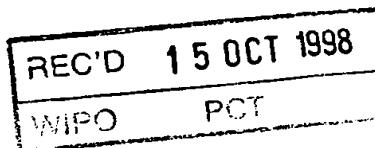
International Application No

PCT/EP 97/03549

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9602642 A	01-02-96	US 5702908 A AU 684194 B AU 2987695 A CA 2195533 A EP 0773996 A	30-12-97 04-12-97 16-02-96 01-02-96 21-05-97
WO 9320238 A	14-10-93	US 5411860 A AT 159985 T AU 681851 B AU 4278893 A CA 2133306 A DE 69315068 D EP 0635068 A JP 7505294 T US 5420263 A US 5550023 A US 5519118 A US 5618921 A US 5708136 A US 5606044 A US 5702903 A	02-05-95 15-11-97 11-09-97 08-11-93 14-10-93 11-12-97 25-01-95 15-06-95 30-05-95 27-08-96 21-05-96 08-04-97 13-01-98 25-02-97 30-12-97
WO 9507934 A	23-03-95	AU 7834894 A CA 2171289 A EP 0719285 A JP 9502725 T	03-04-95 23-03-95 03-07-96 18-03-97

PATENT COOPERATION TREATY

PCT



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-20937/A	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
International application No. PCT/EP97/03549	International filing date (day/month/year) 04/07/1997	Priority date (day/month/year) 05/07/1996	
International Patent Classification (IPC) or national classification and IPC C07K14/00			
Applicant NOVARTIS AG et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 21/01/1998	Date of completion of this report 13. 10. 98
Name and mailing address of the IPEA/ European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Huber, A Telephone No. (+49-89) 2399-8173



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP97/03549

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-40 as originally filed

Claims, No.:

1-23 as originally filed

2. The amendments have resulted in the cancellation of:

the description, pages:
 the claims, Nos.:
 the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application.
 claims Nos. 1-9 (partially).

because:

the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP97/03549

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- no international search report has been established for the said claims Nos. 1-9 (partially).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 3-5, 7-9, 11, 16
	No:	Claims 1, 2, 6, 10, 12-15, 17-23
Inventive step (IS)	Yes:	Claims 3-5, 7-9, 11, 16
	No:	Claims 1, 2, 6, 10, 12-15, 17-23
Industrial applicability (IA)	Yes:	Claims 1-23 (see Section VII)
	No:	Claims

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP97/03549

SECTION III -----

The international search has been restricted to compounds as defined in Claims 3-9 without taking into consideration "derivatives" of said compounds for the reason that said expression introduces an unlimited number of possibilities and as such renders the scope of the claims indefinite and unclear. Accordingly, the preliminary examination is restricted to subject-matter for which a search has been performed, i.e. no examination on "derivatives" of the claimed compounds is performed.

SECTION V -----

1. The present application relates to compounds which are capable of binding to MDM2 and specifically inhibiting or blocking the binding of MDM2 to the p53 protein, the compound being a peptide which comprises the amino acid motif of formula (I).

2. Reference is made to the following documents:

D1: WO - A - 96/02642

D2: WO - A - 9320238

D3: WO - A 95/07934

3. **Novelty (Art. 33(2) PCT):**

- 3.1. The subject-matter of Claims 1 and 2 is not novel with regard to D1. D1 discloses peptides which are able to disrupt or prevent the binding of between p53 and MDM2. The peptides are between 4 and 10 amino acids long and comprise the sequence motif FxxLW. Since the compounds defined in Claims 1 and 2 are only defined by functional features, the peptides of D1 fall under the scope of said claims. The same objection also applies to Claims 10, 12-15 and 17, insofar as they depend on any of Claims 1 or 2.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP97/03549

3.2. The subject-matter of Claims 18-21 and 23 relates to a method for inducing growth arrest or apoptosis in tumor cells, resp. of treating or preventing a hyperproliferative disease, which does not necessarily make use of any of the peptides of Claims 1-9. Therefore, an objection to lack of unity of invention could be raised. However, since no such objection has been raised in the search report and since the subject-matter of said claims lacks novelty with regard to D2 and D1, the IPEA decided not to raise the objection.

The subject-matter of Claims 18-23 concerns methods for inducing growth arrest or apoptosis in tumour cells comprising inhibiting the interaction of MDM2 and p53, resp. a method of treating a hyperproliferative disease.

D2 discloses a method for treating neoplastic cells wherein expression of the MDM2 gene is inhibited by administering antisense oligonucleotides or triple-strand forming oligonucleotides. In addition, p53-derived peptides and DNA encoding such peptides can be administered to tumour cells (see D2, page 10, last paragraph to page 12, first paragraph and Claims 27-29 and 33-40). D2 is therefore regarded as being novelty-destroying for the subject-matter of Claims 18-21 and of Claim 22, insofar as it depends on Claim 2.

D1 provides a method for inhibiting the growth of tumour cells which comprises administering to a tumour cell a DNA molecule encoding an MDM2-binding peptide. The subject-matter of Claims 21 and 22 (insofar as it depends on Claim 2) is therefore not regarded as novel with view to D1.

A method for the treatment of cancer by administering a compound which interferes with the interaction of p53 and MDM2 is also described in D1, see page 11, lines 19-31. Thus, the subject-matter of Claim 23 is anticipated by D1.

3.3. Claim 6 is directed to a peptide of Claim 3 which comprises at least 8 consecutive amino acids of formula (I). D3 discloses peptides which were shown to inhibit IL8 binding to its receptor. At least one of said peptides, namely that shown in Claim 7, comprises eight consecutive amino acids of the peptide having formula (I). It is likely that said peptide is capable of binding to MDM2. Claim 6 therefore lacks novelty with regard to D3.

3.4. Claims 3-5 and 7-9 are directed to peptides which are capable of inhibiting or blocking the binding of MDM2 to p53 and which comprise the amino acid motif of

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP97/03549

formula (I). Said motif contains an amino acid at position R3 which is different from Leu. Peptides derived from p53 which were used in the prior art to inhibit binding of MDM2 to p53 all contain Leu at the respective position. It has surprisingly been found by the present inventors that peptides wherein Leu is replaced by a different amino acid, preferably Tyr, show a significant increase in specific blocking activity over the wildtype p53 peptide sequence.

Claims directed to peptides which are defined by the amino acid sequence of formula (I) are therefore novel and inventive with regard to the prior art.

The same applies to claims concerning uses and processes involving said peptides.

SECTION VII -----

For the assessment of the present Claims 13 and 17-23 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VIII -----

1. Claims 1, 18 and 23 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem, instead of indicating the technical features which are necessary for achieving this result.

2. Claims 18-21 relate to a method for inducing growth arrest in tumor cells. Claims 19, 20 and 21 all include the term "further comprises", which means that the embodiments following said term in the claims are to be understood as additive embodiments. There is, however, no disclosure in the description and it does not seem to make technical sense that antibodies, triple strand forming

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP97/03549

oligonucleotides and DNA expressing a peptide capable of binding to MDM2 are administered at the same time to a cell. The subject-matter of said claims is therefore objected to under Articles 5 and 6 PCT.

PATENT COOPERATION TREATY
PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 4-20937/A	FOR FURTHER ACTION		see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/EP 97/ 03549	International filing date (day/month/year) 04/07/1997	(Earliest) Priority Date (day/month/year) 05/07/1996	
Applicant NOVARTIS AG et al.			

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of **5** sheets.
 It is also accompanied by a copy of each prior art document cited in this report.

1. Certain claims were found unsearchable (see Box I).
2. Unity of Invention is lacking (see Box II).
3. The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 - filed with the international application.
 - furnished by the applicant separately from the international application,
 - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - Transcribed by this Authority
4. With regard to the title,
 - the text is approved as submitted by the applicant.
 - the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - the text is approved as submitted by the applicant.
 - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:

Figure No. _____

 - as suggested by the applicant.
 - because the applicant failed to suggest a figure.
 - because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 1-9

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

In claims 1-2, the compounds are defined only by their capability to bind MDM2, feature not sufficient to allow a complete search.

In claims 2-9, the expression "derivatives thereof" is used in a too broad sense, consequently a complete search under Art 17(2) PCT was not possible. Therefore, the search has been directed to peptides as defined in claims 3-9, without taking in consideration any "derivative thereof".

Moreover, because of the high number of pertinent documents found in the prior art for the subject-matter of claim 6, only a few could be cited.

Remark : Although claims 17-22 and at least in part 10,12,13 and 23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/03549

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07K14/47 C07K14/82 C12Q1/68 C12N15/11 A61K38/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 02642 A (UNIV DUNDEE ; PICKSLEY STEVEN MICHAEL (GB); LANE DAVID PHILIP (GB)) 1 February 1996 see page 3, line 20 - page 4, line 31 see example 3 see claims ---	1-18, 21-23
X	WO 93 20238 A (UNIV JOHNS HOPKINS) 14 October 1993 see claims 27-37 see the whole document ---	1-23 -/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

- *&* document member of the same patent family

2

Date of the actual completion of the international search 11 March 1998	Date of mailing of the international search report 08.04.98
--	--

Name and mailing address of the ISA
 European Patent Office, P.B. 5818 Patenttaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Cervigni, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/03549

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S.M. PICKSLEY ET AL: "Immunochemical analysis of the interaction of p53 with MDM2" ONCOGENE, vol. 9, September 1994, pages 2523-2529, XP002058480 see page 2526 ---	1-10,12
X	J. LIN ET AL.: "Several hydrophobic amino acids in the p53 amino-terminal domain are required for transcriptional activation, binding to mdm-2 and the adenovirus 5 E1B 55-kD protein" GENES AND DEVELOPMENT, vol. 8, no. 10, May 1994, pages 1235-1246, XP002058481 see abstract see table 2 ---	1-10,12
P,X	V. BÖTTGER ET AL: "Identification of novel mdm2 binding peptides by phage display" ONCOGENE, XP002058482 see the whole document see page 2143, column 2, paragraph 4 - page 2143, paragraph 1; figure 5 ---	1-23
X	H. LEE ET AL: "Molecular characterisation of Nos-A" J. BACTERIOL., vol. 173, no. 17, September 1991, pages 5606-5413, XP002058483 * residues 462-471 * see figure 4 ---	3,6
X	WO 95 07934 A (CHIRON CORP) 23 March 1995 see page 3, line 30; claim 7 -----	6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/03549

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9602642 A	01-02-96	US 5702908 A AU 684194 B AU 2987695 A CA 2195533 A EP 0773996 A	30-12-97 04-12-97 16-02-96 01-02-96 21-05-97
WO 9320238 A	14-10-93	US 5411860 A AT 159985 T AU 681851 B AU 4278893 A CA 2133306 A DE 69315068 D EP 0635068 A JP 7505294 T US 5420263 A US 5550023 A US 5519118 A US 5618921 A US 5708136 A US 5606044 A US 5702903 A	02-05-95 15-11-97 11-09-97 08-11-93 14-10-93 11-12-97 25-01-95 15-06-95 30-05-95 27-08-96 21-05-96 08-04-97 13-01-98 25-02-97 30-12-97
WO 9507934 A	23-03-95	AU 7834894 A CA 2171289 A EP 0719285 A JP 9502725 T	03-04-95 23-03-95 03-07-96 18-03-97